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Eldelumab (Anti-interferon- γ -Inducible Protein-10 Antibody) Induction Therapy for Active Crohn's Disease: a Randomised, Double-Blind, Placebo-Controlled Phase IIa Study

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Eldelumab for the treatment of Crohn's disease

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Subject: Clinical trials

Classification: Clinical trials

Non-standard abbreviations

6-MP: 6-mercaptopurine azathioprine

6-TGN: 6-thioguanine

AE: adverse event

anti-TNF: anti-tumour necrosis factor

AZA: azathioprine

CI: confidence interval

CDAI: Crohn's disease activity index

C_{minss}: minimum steady-state plasma drug concentration

hsCRP: C-reactive protein

IP-10: interferon- γ -inducible protein-10

IV: intravenous

MTX: methotrexate

OR: odds ratio

SE: standard error

SES-CD : simplified endoscopic score for Crohn's disease

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Background and aims: This 11-week Phase IIa induction study evaluated the efficacy and safety of eldelumab in patients with active Crohn's disease.

Methods: Adults with Crohn's Disease Activity Index 220–450 were randomised 1:1:1 to placebo or eldelumab 10 or 20 mg/kg intravenously on Days 1 and 8, and alternate weeks thereafter. All patients underwent ileocolonoscopy at baseline. Patients with active inflammation according to the Simplified Endoscopic Score for Crohn's Disease criterion (the originally planned endoscopy cohort) underwent another ileocolonoscopy at Week 11 at the investigator's discretion. All ileocolonoscopies were centrally read. The primary objective was identification of the eldelumab target exposure for induction of remission (absolute Crohn's Disease Activity Index score <150). Rates of clinical response (reduction of ≥ 100 from baseline or absolute score <150 Crohn's Disease Activity Index), remission and endoscopic improvements were also assessed.

Results: 121 patients were randomised. The eldelumab exposure–remission relationship was not significant at Week 11. Numerically higher remission and response rates were reported with eldelumab 20 mg/kg (29.3 and 41.5%, respectively) and 10 mg/kg (22.5 and 47.5%) versus placebo (20.0 and 35.0%). A higher proportion of patients with a baseline Simplified Endoscopic Score for Crohn's Disease >2 who received eldelumab achieved a 50% improvement in score and greater reductions from baseline endoscopy scores overall versus placebo. Adverse events were comparable across treatment groups.

Conclusions: No exposure–remission relationship was seen with eldelumab. Eldelumab induction treatment demonstrated trends towards clinical and endoscopic efficacy. Safety was consistent with that reported previously. ClinicalTrials.gov identifier: NCT01466374.

KEYWORDS: Anti-interferon- γ -inducible protein-10 antibody; Crohn's disease; inflammatory bowel disease

1. Introduction

Crohn's disease is a chronic inflammatory disorder of the gastrointestinal tract of multifactorial aetiology.¹ Crohn's disease can affect all layers of the intestinal wall, leading to the development of ulcers as well as the complications of fistulas and abscesses. This pathology manifests as symptoms such as pain, diarrhoea, vomiting and fatigue, and can result in a requirement for recurrent surgeries, work absenteeism and difficulties with interpersonal relationships.² Crohn's disease has a reported annual incidence of approximately 24 per 100,000 in Europe and 19 per 100,000 in Northern America; incidence rates are increasing globally, particularly in developing countries.³

A number of pharmacological and surgical approaches have been developed for Crohn's disease. Owing to its diverse presentation and pathophysiology, treatment strategies for Crohn's disease are based on the anatomic location of the disorder, disease severity and therapeutic goals, such as treatment of flares and induction or maintenance of remission.^{4,5} In addition, mucosal and histological healing have emerged as potential treatment goals with the development of more specifically targeted medications and individualisation of therapeutic approaches.^{6,7}

Presently, commonly used treatments for Crohn's disease include corticosteroids, 6-mercaptopurine (6-MP), azathioprine (AZA), methotrexate (MTX) and biologics (including anti-tumour necrosis factor [anti-TNF] and anti-integrin agents [natalizumab, vedolizumab]). These medications have a number of limitations, such as a lack of long-term efficacy (corticosteroids) as well as slow onset of action and toxicity (AZA, 6-MP and MTX). While the use of biologics represented a substantial development in the treatment of Crohn's disease compared with traditional oral therapies, remission is achieved by as few as 20–40% of patients and maintained by

only 50% of these individuals at 6 months.⁸ Moreover, increased risks of side effects, including malignancies and opportunistic infections have been reported with biologics.⁹⁻¹²

Interferon- γ -inducible protein-10 (IP-10, also referred to as CXCL10) decreases the survival of gut epithelial cells and mediates trafficking of activated T cells, dendritic cells and monocytes to the inflamed colon.^{13,14} IP-10 expression by intestinal epithelial cells, endothelial cells and immune cells is increased in patients with Crohn's disease,^{15,16} and reduction of IP-10 is a novel therapeutic target in Crohn's disease.^{17,18}

Eldelumab (BMS-936557) is a fully human monoclonal antibody that has been investigated as an induction and maintenance therapy in moderate to severely active ulcerative colitis in Phase II trials.^{19,20} It is hypothesised that by binding to IP-10, eldelumab blocks immune cell migration into the intestinal epithelium and modulates the impact of IP-10 on epithelial cell survival.^{14,21} Efficacy signals for eldelumab in the treatment of ulcerative colitis were observed, particularly among patients who were biologic naïve or receiving concomitant immunosuppressants.²⁰

To date, eldelumab has not been assessed in Crohn's disease. The induction period of the current Phase IIa study was designed to demonstrate dose–response and to evaluate the efficacy and safety of eldelumab in patients with active Crohn's disease.

2. Materials and methods

2.1. Study design and patients

This Phase IIa study (ClinicalTrials.gov Identifier NCT01466374) comprised an 11-week induction period (see online Supplementary Figure 1) and a 12-month exploratory maintenance period. The results of the maintenance period are not yet available and will be reported in a future publication. The study was conducted at 28 sites in seven countries (Belgium, France, Hungary, Israel, Poland, South Africa and the USA) between 15 December 2011 and 3 November 2014. All patients gave written, informed consent and the study was approved by local ethics committees and conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

Eligible patients were ≥ 18 years of age with moderate to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score ≥ 220 and ≤ 450) and disease duration of more than 3 months. The diagnosis of Crohn's disease was confirmed by radiological, endoscopic or histological evidence in the 12 months before screening; if a previous diagnosis had not been made or was deemed inconclusive, diagnosis was confirmed during the screening ileocolonoscopy. In addition, patients included in the trial were required to have active inflammation, indicated by high-sensitivity C-reactive protein (hsCRP) ≥ 5 mg/L, or faecal calprotectin >250 $\mu\text{g/g}$, or a score of 2–3 on the ulcerated surface subscore of the Simplified Endoscopic Score for Crohn's Disease (SES-CD) in at least one of five segments during ileocolonoscopy.

Ileocolonoscopy videos were collected from all included patients at baseline. It was originally planned that the endoscopy cohort would include only patients with an ulceration score of 2–3 in at least one of five bowel segments at baseline but, owing to the small sample size that resulted from this criterion, the endoscopy cohort definition was amended to include patients with a total SES-CD score >2 . Patients

with active inflammation according to the SES-CD criterion (the originally planned endoscopy cohort) underwent another endoscopy at Week 11 at the investigator's discretion. All endoscopies were read in a blinded fashion by a central reader.

To be included in the trial, patients also had to have had an insufficient response or intolerance to one or more of oral prednisone (≥ 40 mg/day for ≥ 2 weeks or ≥ 20 mg/day for ≥ 4 weeks) or budesonide (≥ 9 mg/day for ≥ 2 weeks or ≥ 3 mg/day for ≥ 4 weeks), AZA (≥ 2 mg/kg/day or a therapeutic level of 6-thioguanine [6-TGN]), 6-MP (≥ 1 mg/kg/day or therapeutic level of 6-TGN), MTX (≥ 15 mg/week) and/or a biologic (anti-TNF or natalizumab; at the approved dose).

Key exclusion criteria were a diagnosis of ulcerative colitis or indeterminate colitis, and a diagnosis of Crohn's disease without colonic or ileal involvement. Patients were also excluded if they were suspected of having or had been diagnosed with an intra-abdominal or perianal abscess at screening or had known strictures or stenosis (without an inflammatory component, leading to symptoms of obstruction). In addition, patients were excluded if they had a current requirement for colostomy, ileostomy or total parenteral nutrition, or had previously undergone total proctocolectomy or subtotal colectomy with ileorectal anastomosis. Surgical bowel resection within 6 months of screening, extensive small bowel resection, known short bowel syndrome or previous sclerosing cholangitis were also reasons for study exclusion. In an amendment half way through the study, patients who experienced inadequate response/intolerance to ≥ 3 approved biologics were also excluded. The use of biologics, tacrolimus, cyclosporine, mycophenolate mofetil, D-penicillamine, leflunomide or thalidomide was prohibited within 8 weeks prior to randomisation; use of rituximab was prohibited within 1 year of randomisation.

2.2. Dose selection and randomisation

Based on earlier studies of eldelumab in patients with ulcerative colitis, the 10 and 20 mg/kg doses selected for the induction period in the present study were expected to generate a robust exposure–response relationship.^{19,20} The eldelumab 10 mg/kg dose did not demonstrate consistent efficacy in patients with ulcerative colitis; however, as the present Phase IIa study in Crohn’s disease was a dose-ranging study, and because Crohn’s disease is thought to have a lower inflammatory burden compared with ulcerative colitis, the lower dose of 10 mg/kg was deemed to be appropriate for inclusion.

During the induction period, eligible patients were randomised 1:1:1 to double-blind treatment with eldelumab 10 mg/kg or 20 mg/kg or placebo saline solution. Randomisation was stratified according to patients’ prior inadequate response and/or intolerance to approved biologic therapy (yes/no). Study medication was administered via intravenous (IV) infusion on Days 1 and 8, and every other week thereafter to Day 64. Adverse events (AEs) and vital signs were monitored after completion of infusion; initial observations of infusion reaction associated with an infusion time of 90 minutes resulted in a protocol amendment that extended the study-drug infusion to 3 hours to reduce the occurrence of infusion reactions.

2.3. Efficacy objectives and assessments

2.3.1. Primary objective

The primary objective was to identify the efficacious target exposure (observed minimum steady-state plasma drug concentration [C_{minss}]) for induction. The primary efficacy objective was assessment of eldelumab induction of clinical remission (CDAI <150) as determined by a relationship between eldelumab exposure (C_{minss}) and remission at Week 11.

2.3.2. Secondary and exploratory objectives

Secondary objectives were assessment of clinical response (reduction in CDAI ≥ 100 points from baseline or absolute CDAI score < 150) at Weeks 7 and 11, and clinical remission at Weeks 7 and 11.

A number of exploratory objectives were also assessed during the induction period, including endoscopic response at Week 11 in patients in the endoscopy cohort (defined as $\geq 50\%$ improvement in the SES-CD²²); change from baseline in biomarkers, including hsCRP and faecal calprotectin; and the pharmacokinetics of eldelumab. Subgroup analyses of clinical response and remission in patients with prior insufficient response/intolerance to biologics or patients who were biologic naïve were also assessed. A number of composite endpoints (incorporating both symptomatic and endoscopic findings) were also investigated, including the percentages of patients achieving $\geq 30\%$ decrease in stool frequency and abdominal pain alongside a 3-point decrease in SES-CD or an absolute SES-CD of zero.²³

2.3.3. *Post hoc* analyses

Several *post hoc* analyses were performed in the endoscopy cohort for subgroups with baseline SES-CD score > 2 , ≥ 4 and ≥ 6 . These analyses included an assessment of endoscopic response at Week 11, and the percentages of patients achieving $\geq 30\%$ decrease in stool frequency and abdominal pain and a 3-point decrease in SES-CD or an absolute SES-CD of zero.

2.3.4. Efficacy assessments

The CDAI total score is the sum of eight components with different weighting factors²⁴⁻²⁶; e.g. haematocrit of < 0.47 units in men and < 0.42 units in women has a weighting factor of x6. Lower scores on the CDAI indicate milder disease; severe Crohn's disease is defined as a CDAI score of > 450 .^{24,26} CDAI diaries were

completed by patients for 7 days before each study visit (baseline and Weeks 1, 3, 5, 7, 9 and 11) to allow investigational staff to calculate CDAI scores.

Changes from baseline in endoscopy score and endoscopic response were assessed at Week 11 using centrally read ileocolonoscopy. The SES-CD score comprises four variables (ulcer size, ulcerated surface area, proportion of the affected surface with other lesions and stenosis), scored from 0 (absence of variable) to 3 (most severe manifestation of variable), with the total score consisting of the sum of the four variables for each of the five bowel segments.²⁷

Blood for assessment of hsCRP was drawn at baseline and at Weeks 1, 3, 5, 7 and 11. Patients were required to bring stool samples to office visits for assessment of faecal calprotectin at baseline and Weeks 7 and 11.

2.3.5. Pharmacokinetic assessments

Venous blood samples for serum pharmacokinetic analyses were collected from all patients in this study at baseline, and at Weeks 1, 3, 5, 7 and 11. Pharmacokinetic analyses of eldelumab in human serum were performed using enzyme-linked immunosorbent assays.

2.4. Safety assessments

The incidence and severity of AEs were monitored throughout the study and for up to 56 days after the last dose of study medication. Treatment-related AEs were defined as those possibly, probably or definitely related to the study drug; when details were missing, AEs were presumed to be related to treatment. Acute infusion reactions were defined as any AE that could potentially constitute a reaction to infusion, occurring within 1 hour of infusion completion.

2.5. Statistical analysis

The sample sizes in this study were calculated to provide adequate power for the primary analysis during the induction period (logistic regression modelling to investigate the eldelumab exposure–response [i.e. remission] relationship at Week 11). Based on an assumed placebo remission rate of 15%, it was calculated that to detect an odds ratio (OR) of 2.5 using logistic regression, 40 patients per arm were required to provide 90% power for a one-sided test at $\alpha = 0.05$.

The intent-to-treat population was the primary study population, comprising all patients randomised and administered any study medication. The safety analysis was performed using the safety population, and comprised all patients who received at least one dose of any study medication.

Sequential testing was performed as a multiplicity adjustment; if the primary endpoint was not statistically significant then secondary endpoints were not analysed further. As such, the study was powered only to assess the eldelumab exposure–remission relationship and was not statistically powered to test the efficacy objectives. Baseline demographics and clinical characteristics at randomisation were analysed descriptively. The exposure–remission relationship at Week 11 was modeled by logistic regression with the observed $C_{\min ss}$ as an independent variable. The efficacious target exposure for induction of remission, corresponding OR and 90% confidence interval (CI) were calculated. All patients who discontinued prematurely were considered to be non-responders/non-remitters in binary analyses in this study.

For the statistical analyses of secondary (efficacy) objectives, the percentage of patients who were responders/remitters was analysed using the Cochran–Mantel–Haenszel chi-square test at a one-sided 5% significance level, stratified by prior inadequate response to/intolerance of biologics (yes/no); relative risk and 90% CIs were also calculated.

3. Results

3.1. Patient disposition and demographic characteristics

During the induction period, a total of 121 patients were randomised and treated (see online Supplementary Figure 2). Overall, 80.0, 85.4 and 97.5% of patients completed the study in the eldelumab 10 and 20 mg/kg and placebo groups, respectively. AEs were the reason for discontinuation in five patients in each of the eldelumab 10 and 20 mg/kg arms (12.5 and 12.2% of patients, respectively) and no patients in the placebo arm. AEs leading to discontinuation included: four hypersensitivity reactions (two of which were serious, all occurred in the eldelumab 20 mg/kg arm); two infusion reactions (one each in the eldelumab 10 and 20 mg/kg arms); two serious AEs of exacerbation of Crohn's disease (both in the eldelumab 10 mg/kg arm); one serious AE of peripheral arterial thrombosis (in the eldelumab 10 mg/kg arm); and one serious AE of small intestinal obstruction (in the eldelumab 20 mg/kg arm).

Patient demographics were generally well balanced between treatment groups (Table 1). Sixty-five percent of patients were recruited from Europe, the majority of whom were located in Eastern Europe. The mean duration of Crohn's disease was 9.1 years and the mean CDAI was 317. More than 70% of patients had previously received treatment with corticosteroids and/or immunosuppressants. Furthermore, 63% of patients had previously received biologic therapy, and approximately 40% of patients overall had received treatment with ≥ 2 biologics. More patients in the eldelumab 10 mg/kg group had failed prior corticosteroids or immunosuppressants (80.0 and 85.0%, respectively) compared with patients in the eldelumab 20 mg/kg (75.6 and 68.3%) and placebo groups (62.5 and 72.5%). A higher percentage of patients in the eldelumab 10 mg/kg arm were receiving concomitant immunosuppressants (40.0%) compared with the eldelumab 20 mg/kg and placebo arms (17.1 and 27.5%, respectively). Eighty-one (66.9%) patients were included in

the endoscopy cohort. The baseline characteristics of the patients in the endoscopy cohort were generally similar to those in the overall patient population, with some exceptions: the mean baseline CDAI score was slightly lower across all treatment arms (range 295–308) compared with the overall population (range 310–323), and the proportion of patients who had received prior biologic therapy in the eldelumab 20 mg/kg group was higher (73.9%) compared with the overall population (58.5%; Table 1 and Supplementary Table 1).

3.2. Primary endpoint

The study did not meet its primary endpoint. Logistic regression analysis showed that there was no statistically significant exposure–remission relationship with eldelumab at Week 11 (OR [90% CI] 1.064 [0.958, 1.182]; Figure 1). Optimal exposure was reached with both eldelumab doses in this study and clinical efficacy was maximised.

3.3. Clinical remission and response

Small numerical but non-significant differences were seen at Week 11 between the placebo and active treatment arms in terms of the percentages of patients achieving CDAI remission and response (Figure 2a). Eldelumab 20 mg/kg resulted in the highest rates of CDAI remission, while treatment with eldelumab 10 mg/kg conferred the highest CDAI response rates (treatment differences versus placebo, 9 and 13%, respectively).

Higher rates of CDAI remission and response at Week 11 were reported for the subgroup of biologic-naïve patients treated with eldelumab 10 and 20 mg/kg compared with patients who received placebo (Figure 2b and c). Similarly, CDAI remission and response rates with eldelumab were lower in patients who had received prior biologic treatment compared with biologic-naïve patients (Figure 2b and c).

CDAI reductions over time in eldelumab-treated patients were greater in biologic-naïve patients compared with patients who had received previous treatment with 1–2 biologics (Figure 2d). Reductions in CDAI scores in biologic-naïve patients were particularly pronounced with eldelumab 10 mg/kg and separated from those in patients who were treated with placebo by Week 1. Differentiation in CDAI reductions between patients who were biologic naïve and treated with eldelumab 20 mg/kg and those who received placebo did not become evident until Week 5. CDAI changes with placebo were broadly similar over time regardless of whether patients had previously received biologics.

3.4. Other endpoints

In the endoscopy patient cohort (SES-CD >2 at baseline), treatment with eldelumab 10 and 20 mg/kg resulted in greater mean reductions from baseline in SES-CD compared with placebo (–3.44, –3.57 and –0.94, respectively; Figure 3a). Higher proportions of patients treated with eldelumab 10 and 20 mg/kg versus placebo experienced ≥50% reductions in SES-CD (endoscopic response; Figure 3b).

In the endoscopy patient cohort, improvements in the SES-CD and the percentage of patients achieving ≥50% reduction in SES-CD with eldelumab were similar across the biologic-naïve and biologic-failure subgroups (Figure 3a and b). However, the endoscopy placebo response rates appeared to be greater in the biologic-naïve subgroup compared with patients who had previously received biologics.

Compared with placebo, a substantially higher percentage of patients in the eldelumab 10 and 20 mg/kg arms achieved the composite clinical and endoscopy endpoint (≥30% decrease in stool frequency and abdominal pain plus a 3-point decrease in SES-CD/SES-CD of zero; Figure 4). Composite placebo rates for both the biologic-naïve and biologic-failure subgroups were low (11.1% and 5.9%, respectively). Composite response rates were significantly higher in both of the

eldelumab treatment arms compared with placebo in the overall population as well as in the biologic-naïve and biologic-failure subgroups. The difference in response rates between the eldelumab treatment arms and the placebo arm was higher when assessed using the composite endpoint compared with either of the clinical or endoscopic endpoints alone.

In the *post hoc* sensitivity analyses, using an increasingly more stringent requirement for the baseline endoscopic disease activity (total SES-CD ≥ 4 or ≥ 6 , compared to >2) did not result in a greater effect size using various endoscopic and composite endpoints (Supplementary Table 2).

There was little difference between the treatment groups in terms of change in hsCRP or faecal calprotectin in this study. Mean (standard error [SE]) change from baseline in hsCRP at Week 11 was 4.6 (2.4), -3.6 (2.8) and 3.6 (4.0) mg/L in the eldelumab 10 and 20 mg/kg and placebo arms, respectively. Mean (SE) change in faecal calprotectin was -97.3 (130.6), -101.4 (88.2) and -100.7 (51.0) $\mu\text{g/g}$, respectively.

3.5. Safety

Safety data for the induction period are summarised in Table 2. Treatment-related AEs were experienced by 30.0% (12/40), 39.0% (16/41) and 17.5% (7/40) of patients in the eldelumab 10 and 20 mg/kg and placebo groups, respectively. Headache was the most commonly reported treatment-related AE overall, occurring in 2 patients (5%) in each group. Serious gastrointestinal AEs occurred in 2 patients in each group. Other serious AEs were hypersensitivity (2 patients in the eldelumab 20 mg/kg arm), viral gastroenteritis (1 patient in the eldelumab 20 mg/kg arm) and peripheral artery thrombosis (1 patient in the eldelumab 10 mg/kg arm). The majority of AEs were mild to moderate in intensity.

A higher proportion of patients (35.0%) in the placebo group reported a system organ class AE of infection/infestations compared with the eldelumab 10 and 20 mg/kg groups (22.5 and 26.8%, respectively).

Compared with the placebo group, more patients receiving eldelumab 10 and 20 mg/kg experienced an infusion reaction (0/40 patients, 4/40 [10.0%] patients and 11/41 [26.8%] patients, respectively). All of the infusion events in the eldelumab 10 mg/kg arm were mild to moderate in intensity; three events of hypersensitivity in the eldelumab 20 mg/kg arm were severe (all observed before the protocol amendment).

4. Discussion

This Phase IIa study explored the exposure–remission relationship of eldelumab in Crohn’s disease. The primary endpoint was not met as no significant exposure–remission relationship was seen at Week 11, indicating that at the doses of 10 and 20 mg/kg studied, clinical efficacy had been maximised. However, during the induction period, eldelumab demonstrated trends towards clinical activity in Crohn’s disease, particularly among patients who were biologic naïve. Because the primary endpoint was not met, these findings should be considered exploratory, despite the fact that the 90% CI did not cross zero. This observation is consistent with other recent Crohn’s disease studies in which clinical response was more robust in biologic-naïve versus biologic-failure populations.²⁸⁻³⁰ In this study, substantial treatment differences in terms of the rates of CDAI response and remission with eldelumab in biologic-naïve patients were driven by the greater clinical efficacy of eldelumab in this subgroup (in subanalyses of remission and response) but also by lower rates of placebo response in this subgroup (response subanalysis only). High placebo response rates have been seen previously in inflammatory bowel disease trials of biologic therapies³¹⁻³³ and, as shown by the variable placebo response rates reported here, it is difficult to control for this phenomenon. While significant effort was expended on ensuring selection of patients with true inflammatory disease (via requirements for elevations in hsCRP, faecal calprotectin and/or endoscopic lesions), this study is the first to indicate that endpoint selection, in particular the use of a composite endpoint encompassing both clinical and endoscopic components, may also be effective for controlling placebo response rates.

This was the first placebo-controlled, prospective endoscopy study with central reading in patients with moderate to severely active Crohn’s disease and therefore substantially increases the current evidence base regarding the operational

characteristics of endoscopy scoring in this population. In contrast with the clinical findings, equal endoscopic activity was observed with eldelumab in both the biologic-naïve patients and in patients who had received biologic treatment previously. The placebo endoscopic improvement in the biologic-naïve group appears to be higher than the biologic-failure group, in whom almost no endoscopic improvements were observed; this could be due to the natural waxing–waning of disease resulting in spontaneous mucosal improvement in the biologic-naïve group who, at baseline, had shorter disease duration and milder endoscopic disease. The present study was not powered to investigate the endoscopic endpoints or the subpopulation analyses statistically and therefore it is not possible to comment on the significance of our findings. Given that this is the first study to have used centrally read ileocolonoscopy in a mixed Crohn's disease population comprising both patients who were biologic naïve and those who had previously been treated with biologics, confirmation of these endoscopic results requires further exploration in future studies.

Clinical symptoms and endoscopic activity in Crohn's disease correlate only weakly and therefore it is perhaps not surprising that clinical and endoscopic response with eldelumab differ with regard to prior biologic use status.³⁴ Given the lack of correlation between clinical and endoscopic endpoints, a composite endpoint requiring both clinical and endoscopic improvement in a given patient may be a better indicator of therapeutic effectiveness.²³ In the *post hoc* composite endpoint analysis conducted here, a patient was considered a responder only if a 30% improvement in clinical symptoms (abdominal pain and stool frequency) was accompanied by a 3-point decrease in SES-CD score or an absolute SES-CD score of zero. In this analysis, significant treatment differences between eldelumab and placebo were observed in both the biologic-naïve and biologic-failure subgroups, with very low placebo response rates in both populations. Subgroup analysis by baseline SES-CD score in the endoscopy cohort (baseline SES-CD >2) yielded similar results.

Future studies in patients with Crohn's disease with centrally read endoscopy should further examine the validity of this approach.

In an effort to assess whether the severity of endoscopic disease activity at baseline might affect the observed treatment size, subgroup analyses with increasing baseline total SES-CD score were conducted. Baseline SES-CD scores of >2 , ≥ 4 or ≥ 6 did not appear to have a significant impact on the observed effect size of change in SES-CD, endoscopic response as defined by 50% decrease in SES-CD, or an endoscopic and clinical composite endpoint. These exploratory observations should be confirmed in future studies with a larger sample size.

No new safety signals were observed with eldelumab. Most AE-led discontinuations with eldelumab were due to infusion reactions, the frequency and severity of which diminished after extension of the infusion period from 90 minutes to 3 hours following a protocol amendment. The occurrence of infections was not increased with eldelumab compared with placebo.

In conclusion, clinical efficacy for eldelumab was maximised at the study doses of 10 and 20 mg/kg; however, the primary endpoint of the trial was not achieved. Clinical response and remission with eldelumab were more pronounced in subgroups of patients who were biologic naïve, while endoscopic improvements with eldelumab were similar across the biologic-naïve and biologic-failure subgroups. Composite endpoints comprising both clinical and endoscopic scores provided the most robust discrimination between both eldelumab doses and placebo. Safety signals were consistent with those reported previously for eldelumab.

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William J Sandborn, Pranab Mitra and Allison Luo were involved in the conception and design of the study. William J Sandborn, Paul Rutgeerts, Jean-Frédéric Colombel, Subrata Ghosh, Robert Petryka, Bruce E Sands, Pranab Mitra and Allison Luo analysed and interpreted the study data. WJS was the Principal Investigator for this study and PR was the central endoscopy reader. All authors critically reviewed the content of this manuscript and approved the final version for submission.

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Conflicts of interests

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Table 1. Baseline demographics and clinical characteristics.

Characteristic	Placebo (<i>n</i> = 40)	Eldelumab		Total (<i>N</i> = 121)
		10 mg/kg (<i>n</i> = 40)	20 mg/kg (<i>n</i> = 41)	
Mean age (SD), years	37.3 (13.1)	35.8 (13.0)	35.4 (13.1)	36.2 (13.0)
Mean weight (SD), kg	69.6 (19.4)	75.1 (22.8)	70.2 (14.0)	71.6 (19.0)
Female, <i>n</i> (%)	22 (55.0)	17 (42.5)	21 (51.2)	60 (49.6)
Geographic region, <i>n</i> (%)				
North America	11 (27.5)	12 (30.0)	13 (31.7)	36 (29.8)
Europe	28 (70.0)	26 (65.0)	25 (61.0)	79 (65.3)
Eastern Europe	14 (35.0)	18 (45.0)	16 (39.0)	48 (39.7)
Western Europe	14 (35.0)	8 (20.0)	9 (22.0)	31 (25.6)
South Africa	1 (2.5)	2 (5.0)	3 (7.3)	6 (5.0)
Mean (SD) duration of CD, years	9.5 (8.8)	8.7 (8.4)	9.3 (8.3)	9.1 (8.5)
Mean (SD) CDAI score	323 (67)	310 (59)	317 (57)	317 (61)
Prior therapy, <i>n</i> (%)				
Corticosteroids	25 (62.5)	32 (80.0)	31 (75.6)	88 (72.7)
Immunosuppressants	29 (72.5)	34 (85.0)	28 (68.3)	91 (75.2)
Biologic	27 (67.5)	25 (62.5)	24 (58.5)	76 (62.8)
1–2 biologics	22 (55.0)	21 (52.5)	21 (51.2)	64 (52.9)
≥3 biologics	5 (12.5)	4 (10.0)	3 (7.3)	12 (9.9)
Concomitant corticosteroid, <i>n</i> (%)	22 (55.0)	21 (52.5)	19 (46.3)	62 (51.2)
Mean oral dose (mg/day)	23.1	22.9	23.1	23.0
Mean budesonide dose (mg/day)	7.5	8.1	9.0	8.2

Concomitant immunosuppressant, <i>n</i> (%)	11 (27.5)	16 (40.0)	7 (17.1)	34 (28.1)
Mean faecal calprotectin, µg/g (SD)	647.0 (571.3)	564.0 (678.8)	505.6 (388.8)	571.7 (556.4)
Mean serum hsCRP, mg/L (SD)	23.4 (26.8)	13.8 (19.8)	15.0 (23.2)	17.4 (23.6)

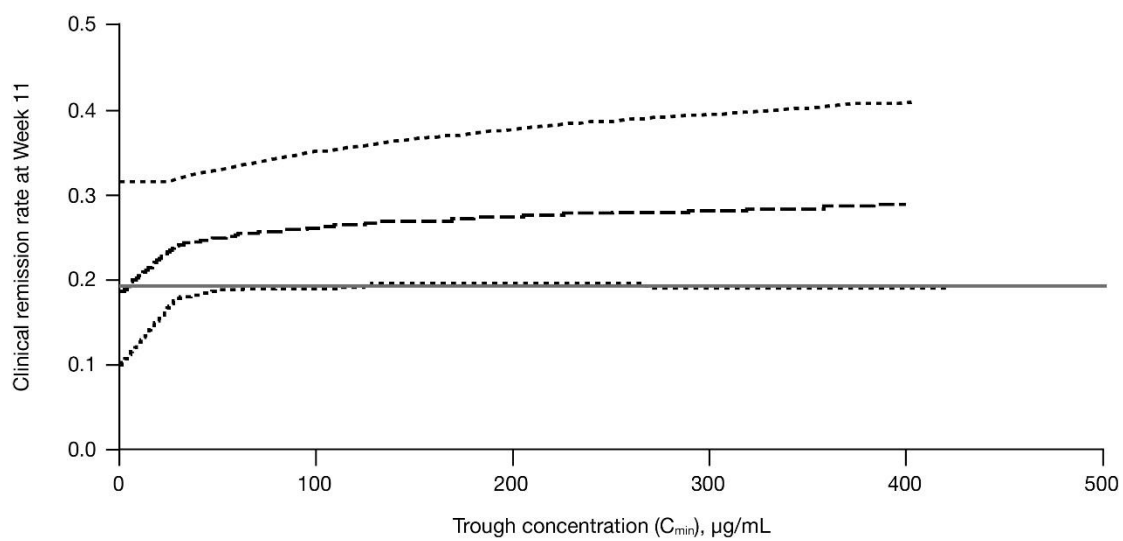
CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; hsCRP, high-sensitivity C-reactive protein SD, standard deviation.

Table 2. Overall summary of adverse events.

Safety parameter	Number (%) of patients		
	Placebo (<i>n</i> = 40)	Eldelumab 10 mg/kg (<i>n</i> = 40)	Eldelumab 20 mg/kg (<i>n</i> = 41)
Deaths	0	0	0
SAEs	2 (5.0)	3 (7.5)	4 (9.8)
Treatment-related SAEs	0	1 (2.5)	3 (7.3)
AEs	31 (77.5)	26 (65.0)	24 (58.5)
Treatment-related AEs	7 (17.5)	12 (30.0)	16 (39.0)
AEs resulting in discontinuation	0	5 (12.5)	5 (12.2)
Infections and infestations	14 (35.0)	9 (22.5)	11 (26.8)
Acute infusion reactions ^a	0	4 (10.0) ^b	11 (26.8) ^c

^aPotentially infusion-related AEs occurring from the start of study drug infusion until 1 hour after the end of infusion; ^ball events were mild to moderate; ^c3 events of 'hypersensitivity' were severe, all observed prior to protocol amendment.

AE, adverse event; SAE, serious adverse event.

Figure 1 Exposure–remission analysis

The average trough concentration is based on mean of Days 36, 50, and 78. Steady state was reached at Day 36. The flat black line denotes the clinical remission rate for all placebo subjects at Week 11. Probability of clinical remission, 90% CI bands, and odds ratio are based on model with log2-transformed trough data

Figure 2(A) Week 11 clinical remission and response. **(B)** Clinical remission by prior biologic use status. **(C)** Clinical response by prior biologic use status. **(D)** CDAI change over time according to prior biologic use. CI, confidence interval; CDAI, Crohn's Disease Activity Index.

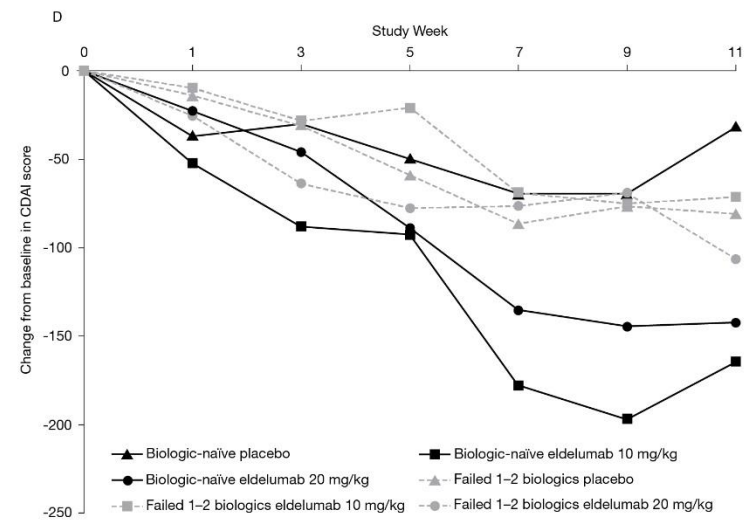
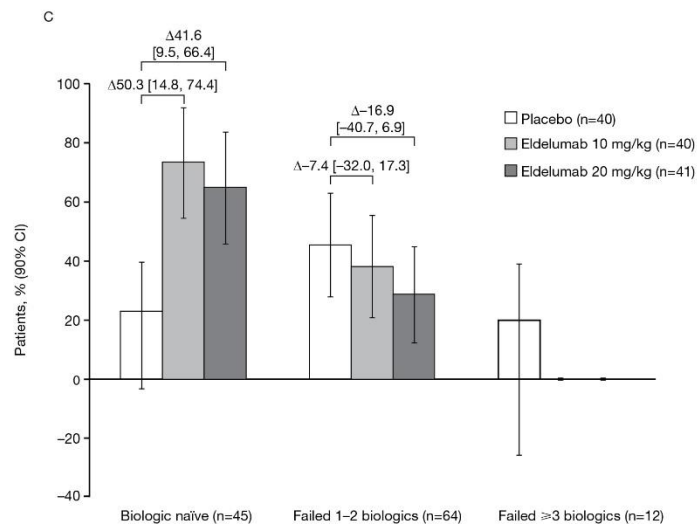
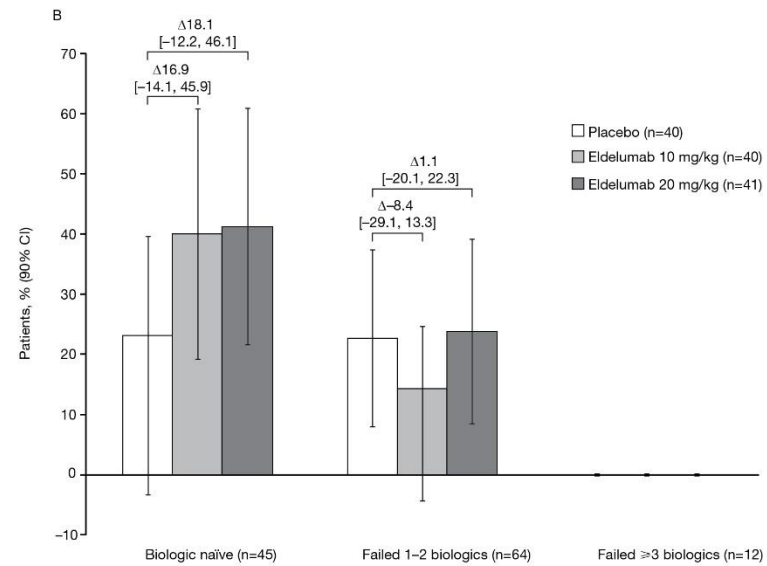
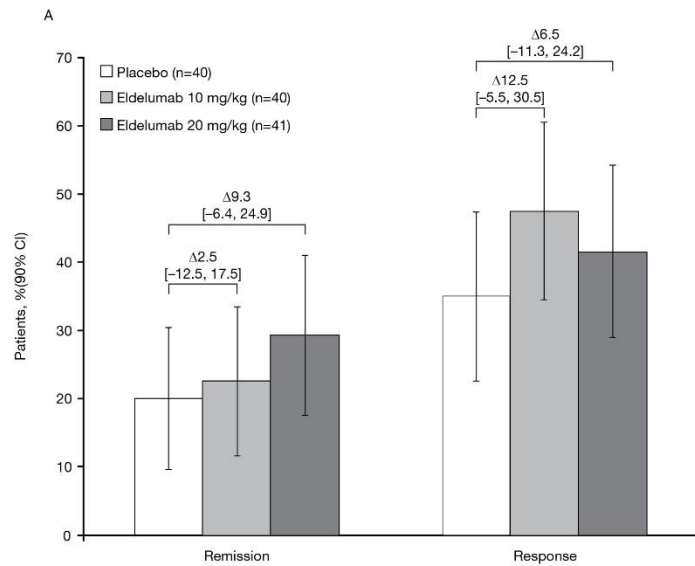


Figure 3 (A) Change from baseline in Simplified Endoscopic Score for Crohn's disease. **(B)** Percentage of patients with $\geq 50\%$ decrease from baseline in Simplified Endoscopic Score for Crohn's disease. SD, standard deviation; SES-CD, Simplified Endoscopic Score for Crohn's disease. CI, confidence interval; SES-CD, Simplified Endoscopic Score for Crohn's disease.

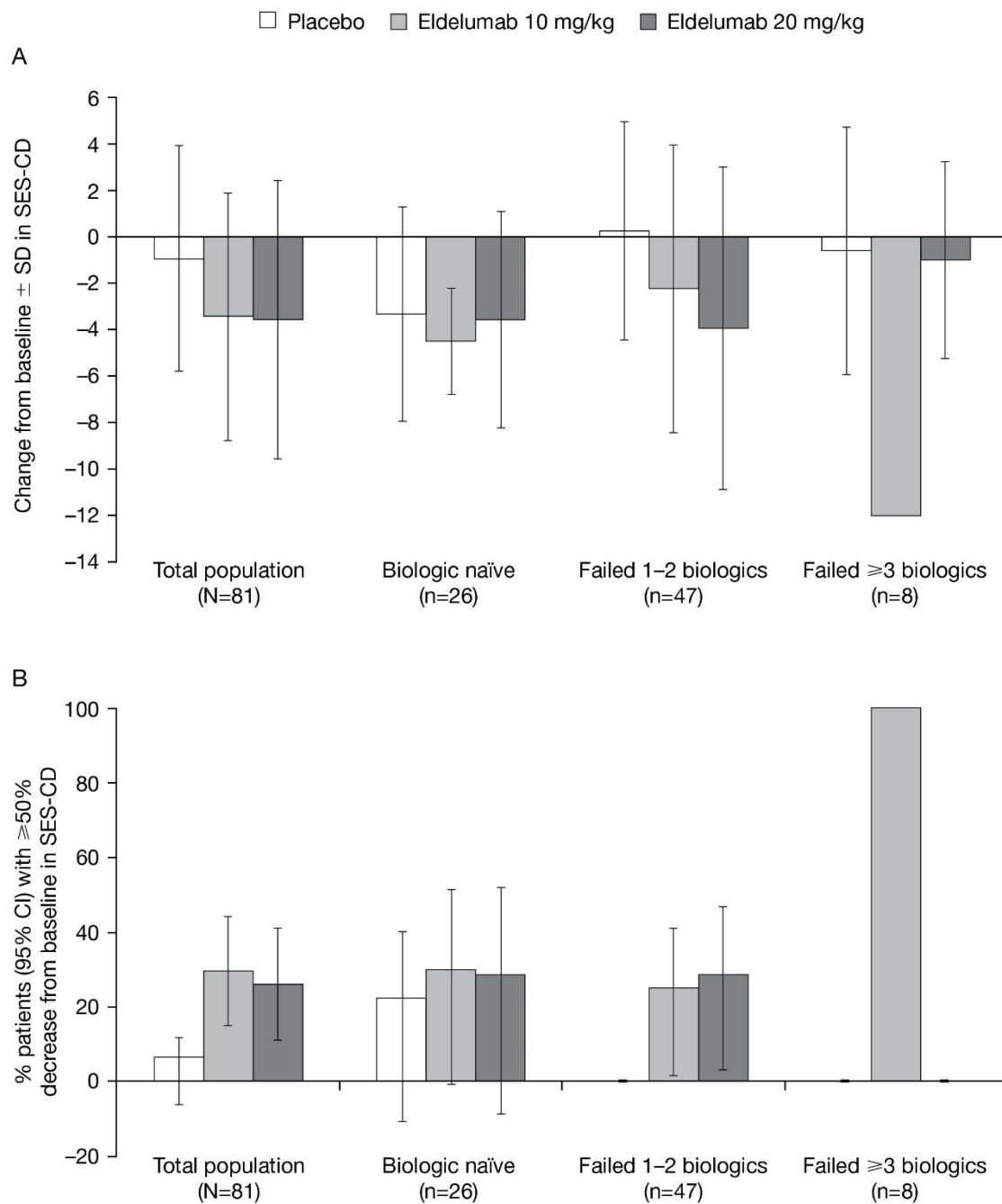
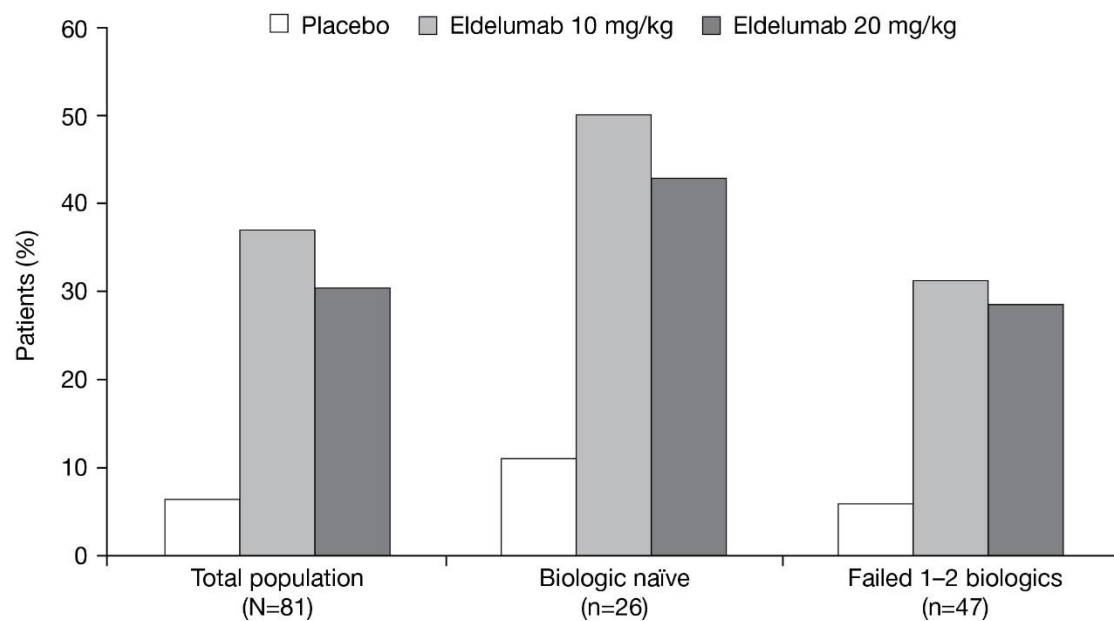


Figure 4 Proportion of patients achieving composite response.*

*Defined as $\geq 30\%$ decrease in stool frequency and abdominal pain plus a 3-point decrease in SES-CD or an SES-CD of 0. Population included all patients with SES-CD >2 at baseline with a post-baseline endoscopy score.

SES-CD, Simplified Endoscopic Score for Crohn's Disease.



Supplementary Table 1. Baseline demographics and clinical characteristics for patients ($n = 81$) with both a baseline SES-CD score >2 and a follow-up SES-CD score

Characteristic	Placebo	Eldelumab	Eldelumab
	($n = 31$)	10 mg/kg ($n = 27$)	20 mg/kg ($n = 23$)
Mean age (SD), years	36.8 (13.9)	35.3 (13.3)	34.9 (12.0)
Mean age ≥ 65 years, n (%)	1 (3.2)	0 (0.0)	0 (0.0)
Mean weight (SD), kg	75.0 (27.3)	98.5 (61.5)	88.2 (49.9)
Female, n (%)	16 (51.6)	10 (37.0)	14 (60.9)
Race, white, n (%)	29 (93.6)	24 (88.9)	22 (95.7)
Mean (SD) CDAI score	308 (72)	295 (57)	302 (65)
Anti-TNF inadequate responder, n (%)	20 (64.5)	17 (63.0)	17 (73.9)

CDAI, Crohn's Disease Activity Index; SD, standard deviation; TNF, tumour necrosis factor

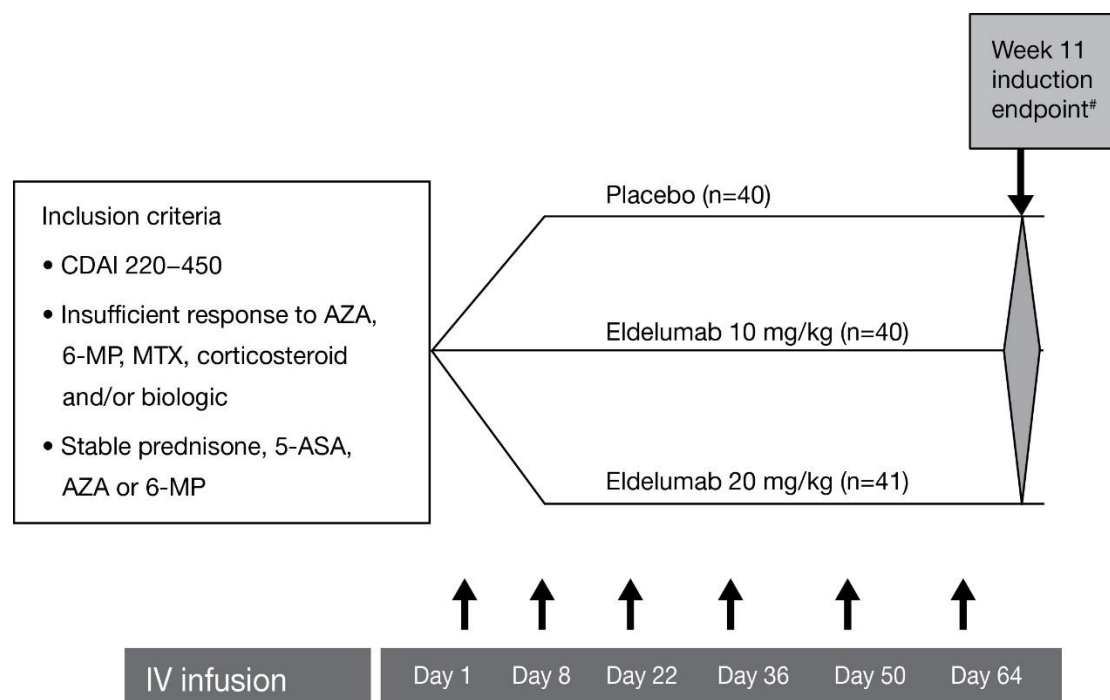
Supplementary Table 2. *Post hoc* analyses of patients with both a baseline SES-CD score >2 and a follow-up SES-CD score at Week 11 ($n = 81$)

		Eldelumab	Eldelumab
	Placebo	10 mg/kg	20 mg/kg
<i>Post hoc</i> analysis	($n = 31$)	($n = 27$)	($n = 23$)
Mean (SD) change from baseline SES-CD for patients [n] with:			
Baseline SES-CD >2	-0.94 (4.87) [31]	-3.44 (5.32) [27]	-3.57 (5.98) [23]
Baseline SES-CD ≥ 4	-0.06 (4.45) [31]	-3.58 (5.38) [26]	-3.62 (6.27) [21]
Baseline SES-CD ≥ 6	0.00 (4.57) [29]	-3.67 (5.58) [24]	-4.32 (6.11) [19]
% Patients (n/N) with $\geq 30\%$ decrease in both liquid stools and abdominal pain and either a decrease from baseline SES-CD ≥ 3 or a SES-CD score of 0 for patients with:			
Baseline SES-CD >2	6.5 (2/31)	37.0 (10/27)	30.4 (7/23)
Baseline SES-CD ≥ 4	6.5 (2/31)	38.5 (10/26)	33.3 (7/21)
Baseline SES-CD ≥ 6	6.9 (2/29)	41.7 (10/24)	36.8 (7/19)
% Patients (n/N) with 50% decrease from baseline SES-CD for patients with:			
Baseline SES-CD >2			

Baseline SES-CD ≥ 4	6.5 (2/31)	29.6 (8/27)	26.1 (6/23)
Baseline SES-CD ≥ 6	6.5 (2/31)	30.8 (8/26)	19.1 (4/21)
	6.9 (2/29)	29.2 (7/24)	21.1 (4/19)

SD, standard deviation; SES-CD, Simplified Endoscopic Score for Crohn's Disease;

Supplementary Figure 1. Study design



ASA, aminosaliclate; AZA, azathioprine; CDAI, Crohn's Disease Activity Index; IV, intravenous; MP, mercaptopurine; MTX, methotrexate.

ASA, aminosaliclate; AZA, azathioprine; CDAI, Crohn's Disease Activity Index; IV, intravenous; MP, mercaptopurine; MTX, methotrexate.

Supplementary Figure 2. Flow chart of patient disposition in the study

